

Importance of cell-cell contact in the therapeutic benefits of cardiosphere-derived cells.

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Public Summary:

Cardiosphere-derived cells (CDCs) effect therapeutic regeneration after myocardial infarction (MI) both in animal models and in humans. Here, we test the hypothesis that cell-cell contact plays a role in mediating the observed therapeutic benefits of CDCs, above and beyond conventional paracrine effects. Human CDCs or vehicle were injected into immunodeficient (SCID) mouse hearts during acute MI. CDC transplantation augmented the proportion of cycling (Ki67(+)) cardiomyocytes and improved ventricular function. CDC-conditioned media only modestly augmented the percentage of Ki67(+) cardiomyocytes (>control but <CDCs), but did not improve pump function. When neonatal rat ventricular myocytes (NRVMs) were cocultured with human CDCs in vitro, the percentage of cycling NRVMs (Ki67(+) or BrdU(+) nuclei) increased relative to solitary NRVM culture. To further dissect the relative contributions of soluble factors versus contact-dependent mechanisms, we compared CDCs grown with NRVMs in a transwell contact-free system versus admixed coculture. The percentage of cycling NRVMs was higher in admixed coculture than in the contact-free system. Pretreatment with inhibitors of MEK and PI3K, or with beta1 integrin neutralizing antibody, blocked the ability of CDCs to promote myocyte cycling. While conditioned media are not inert, direct apposition of CDCs to cardiomyocytes produces greater enhancement of cardiomyocyte proliferation in vitro and in vivo, and improves function post-MI. Intact cardiomyocyte beta1 integrin signaling is necessary for the contact-dependent cardioproliferative effects of CDCs

Scientific Abstract:

Cardiosphere-derived cells (CDCs) effect therapeutic regeneration after myocardial infarction (MI) both in animal models and in humans. Here, we test the hypothesis that cell-cell contact plays a role in mediating the observed therapeutic benefits of CDCs, above and beyond conventional paracrine effects. Human CDCs or vehicle were injected into immunodeficient (SCID) mouse hearts during acute MI. CDC transplantation augmented the proportion of cycling (Ki67(+)) cardiomyocytes and improved ventricular function. CDC-conditioned media only modestly augmented the percentage of Ki67(+) cardiomyocytes (>control but <CDCs), but did not improve pump function. When neonatal rat ventricular myocytes (NRVMs) were cocultured with human CDCs in vitro, the percentage of cycling NRVMs (Ki67(+) or BrdU(+) nuclei) increased relative to solitary NRVM culture. To further dissect the relative contributions of soluble factors versus contact-dependent mechanisms, we compared CDCs grown with NRVMs in a transwell contact-free system versus admixed coculture. The percentage of cycling NRVMs was higher in admixed coculture than in the contact-free system. Pretreatment with inhibitors of MEK and PI3K, or with beta1 integrin neutralizing antibody, blocked the ability of CDCs to promote myocyte cycling. While conditioned media are not inert, direct apposition of CDCs to cardiomyocytes produces greater enhancement of cardiomyocyte proliferation in vitro and in vivo, and improves function post-MI. Intact cardiomyocyte beta1 integrin signaling is necessary for the contact-dependent cardioproliferative effects of CDCs.

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